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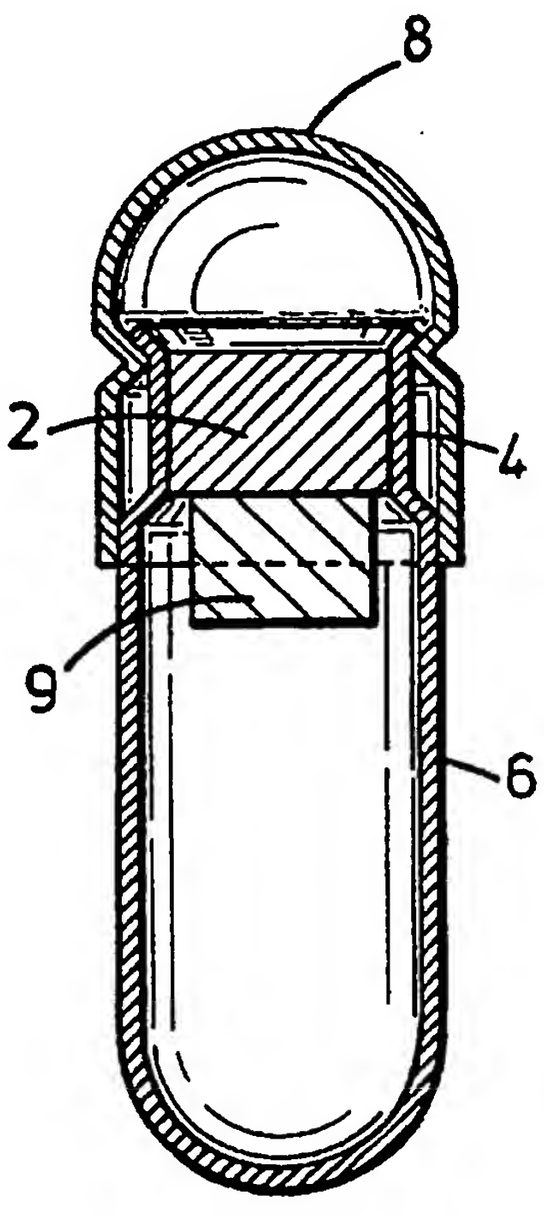
(57) Abstract

A controlled release capsule for delivering a unit dosage of an active material to a patient at a predetermined time following administration comprises a male hydrogel plug (2) engaged in the neck (4) of a female body (6). The unit dosage in solid form is attached as a tablet (9) to the inside end of the plug, or is provided in a recess (12) therein. When the device is placed in an aqueous environment (e.g. the gastrointestinal tract), the hydrogel plug swells and disengages after a predetermined time carrying with it the unit dosage, which is thus effectively delivered from within the female body and dissolution in the aqueous liquid is promoted.



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DISPENSING DEVICE

TECHNICAL FIELD

The present invention relates to a controlled release capsule for delivering active materials, which comprises a male member engaged within a female body; a water-swellable material being provided which swells so as to disengage the female body upon exposure to an aqueous medium. The active material may be delivered to a patient at a chosen time (e.g. 0.5 to 12 hours) following administration.

BACKGROUND

International patent specification WO90/09168 discloses a device of this type which comprises a water-swellable male plug engaged within a female body. A pharmaceutically active material is contained within the device. When the capsule is exposed to water, the male hydrogel plug swells and eventually disengages itself from the female body, thereby allowing the pharmaceutically active material contained within the device to be released. It has been found that the time taken to release the pharmaceutical material is predictable and reproducible, so that the device may be used to release pharmaceutically active materials within the body of a patient after a predetermined time interval. This may, for example, be useful in the treatment of medical

conditions where it is desirable to administer a pharmaceutically active material to the patient sometime through the night (while the patient is asleep) so as to provide a desired level of the drug in the patient in accordance with his needs, for example during the night or when he awakes. It may also be useful to allow dosing of materials at a predetermined point as the capsule passes through the gastro-intestinal tract, for example in the colon.

Patent specification W092/13521 (Alza Corporation) describes fluid-imbibing dispensing devices for delayed delivery of an active agent, which include an expansion means which absorbs fluid from a surrounding environment. The dispensing device comprises a housing having first and second wall sections telescopically engaged with each other, particularly a capsule having a hollow cap and a hollow body. Either the cap or the body is in the form of a male section fitted inside the open end of the other female section. The expansion means is contained within the device and expands as it absorbs fluid, forcing apart the two sections of the device so as to open the device. The expansion means may be a swellable polymer or an osmotic formulation which swells as it absorbs fluid. In order to allow fluid to come into contact with the expansion means contained within the device, one of the wall sections adjacent to the expansion means is fluid-permeable. After the sections are disengaged, fluid

enters the device and comes into contact with the active agent contained within the device, thereby dispensing the active agent into the fluid.

Typically, the pharmaceutically active material contained within the body of the device is in the form of powder or granules. In order for the release time to be well controlled, it is desirable that the pharmaceutically active material is released from the body promptly once the hydrogel plug has been ejected. As set out in WO90/09168, in many applications a pulse of drug at a desired time is required.

A particular application of the controlled release device is release of pharmaceutically active material into the colon. In the colon portion of the gastro-intestinal tract, the waste material contained therein has a particularly high solids content and a particularly low water content. This exacerbates the problem of effectively releasing the contents of the controlled release device into the surrounding fluid so that it becomes available for absorbtion into the patient's system. The relatively low water content means that a minimal amount of water is available for flushing or dissolving the pharmaceutically active material from within the controlled release device. Furthermore, the high solids content means that there is a relatively low degree of agitation within the colon, so that there is a reduced likelihood of the contents of the controlled

release device being expelled by movement of the device within the gastro-intestinal tract.

It is an object of the present invention to address these problems.

SUMMARY OF THE INVENTION

The present invention provides a controlled release capsule for delivering an active material, which comprises a male member engaged within a neck portion of a female body; the capsule including a water-swellable material which swells so as to disengage the female body upon exposure of the capsule to an aqueous medium; and a unit dosage of said active material supported on either the male member or the female body, and the other thereof protecting the unit dosage from the aqueous medium prior to disengagement.

In a particular embodiment the capsule comprises a male plug engaged within a female body; the male plug being formed from a water-swellable material which swells so as to disengage the female body upon exposure to an aqueous medium and a unit dosage of active material supported on the male plug, the female body surrounding the unit dosage and protecting it from the aqueous medium prior to disengagement.

The principle of the present invention is that the active material is associated with the male plug and therefore becomes detached from the body and subject to

the surrounding aqueous environment on disengagement of the plug. Thus, delivery of the active material from the capsule occurs at substantially the same time as the plug is ejected, thereby substantially avoiding any problems associated with complete emptying of the active material from the capsule.

In one form of the invention, the active material is provided within a recess in the inside end of the plug (i.e. that which faces the body). Preferably, the recess is centrally located in the rear face of the plug. The recess may be formed by drilling into the rear face of the plug, for example using a laser or mechanical drill, or by moulding. Typically, the recess is up to 4mm in diameter, usually 2 to 3 mm in diameter; and up to 2mm, preferably up to 1.7mm deep. The dimensions will vary depending on the size of the plug and the amount of active material to be administered.

It has been found that the recess size can be up to 50% of the diameter of the plug and up to 50% of the length, though both should not approach the upper end of these ranges at the same time.

More than one recess may be provided in the rear of the plug.

The recess might also be in the form of one or more channels formed in the end of the plug. The channels might be in the form of a series of parallel channels, concentric circles, a grid pattern or other such arrangement.

The recess may be loose filled with powder, pellets or granules or may be filled with a liquid, paste or melted solid material.

In order to retain the pharmaceutically active material in place, the recess is preferably sealed with a water-soluble material, such as gelatin or polyvinylpyrrolidone paste.

In this way, tiny amounts of active material may be conveniently delivered.

Where the pharmaceutically active material is in a solid form, it is possible that the solid material (e.g. in the form of a cylinder) may project out beyond the surface of the plug.

It is found that during swelling of the hydrogel plug, the recess tends to become distorted, such that the mouth of the recess is enlarged. For example, during hydration of the plug, a cylindrical recess may become slightly frustro-conical. This may be advantageous in that it facilitates ejection of the pharmaceutically active material from the plug and expedites exposure to the surrounding aqueous medium. If desired, the effect may be accentuated by initially forming the recess in a frustro-conical or other outwardly tapering configuration.

The pharmaceutically active material may be any of those disclosed in W090/09168. The capsule body may be bulked out with an inert material, such as lactose, or may be provided with an additional or different active

material depending on the desired dosage regime. The body might also contain a material which expands in the presence of water (such as hydrogel powder or a swellable disintegrant material) and pushes the plug away from the body after disengagement, so assisting dissolution of the active material.

In another form of the invention, the pharmaceutically active material is adhered to the rear face of the hydrogel plug. Generally, the active material is in a solid or other suitable dosage form, such as a tablet, granules and hard or soft capsules. This form of the invention is particularly advantageous where larger amounts of pharmaceutical formulation have to be administered. The maximum size of solid material on the back of the plug is, of course, limited by the available volume of the capsule body. However, close tolerances between the solid material and the body should be avoided in order to facilitate complete disengagement of the plug and pharmaceutically active material from within the capsule body. Preferably, the volume of solid material is less than 50% of the available (i.e. that remaining after the plug has been inserted) body volume.

Since the solid material on the back of the plug becomes immediately exposed on its sides and free end to the aqueous surroundings, a rapid delivery time and complete emptying of the active material from the body is possible. However, other release profiles may be provided

and these may depend on the formulation of the dosage, such as freeze dried tablet, gastroresistant dose, sustained release tablet, pure active etc. Generally, the solid material, such as a tablet, is arranged to dissolve or disintegrate on exposure to aqueous medium. Again, the pharmaceutically active material may be any of those disclosed in W090/09168 without being limited to these.

The solid active material may be adhered to the plug using an adhesive which is water soluble or water-insoluble. However, the adhesive should be arranged so that the active material is retained on the back of the plug, even when the plug becomes hydrated, until after disengagement of the plug. Suitable adhesives include polyvinylpyrrolidone, and conventional film formers; pH sensitive polymers may also be used, as well as gelatin - glycerol mixtures. Enteric coatings may be applied.

The invention also relates to a corresponding process of filling the capsule which comprises storing the caps and bodies separately, introducing the plug and dose of active material into the neck of the body, and fitting a cap over the open end of the body.

Thus, the proposed arrangement ensures that the pharmaceutically active material becomes ejected into the gastrointestinal fluid together with the hydrogel plug as the plug becomes disengaged. If required, a sharp predictable pulse (or other desired release profile) of pharmaceutically active material is thus achieved.

In another embodiment, the male member is a hollow member closed at one end, whose opposite open end engages within the neck of the female body. A water-swellable material is provided within the controlled release device which serves to disengage the female body after a pre-determined time, by forcing the male member and the female body apart as the material swells in the presence of water. The swellable material inside the controlled release device may be an osmagent or an osmopolymer. Such an arrangement is disclosed in patent specification W092/13521. In order to allow water to enter the controlled release device and to contact the water-swellable material a portion of the wall of the device adjacent thereto is preferably semi-permeable, that is to say it is permeable to the passage of water into the device but impermeable to release of other substances from within the device.

In particular, the unit dosage of active material may be attached to a movable partition of the type provided in W092/13521 which moves within the female body as the water-swellable material expands to disengage the male member and the female body.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Embodiments of the present invention will now be described by way of example only in conjunction with the drawings wherein;

Figure 1 is a sectional elevation of a first embodiment having a tablet on the back of the plug; and

Figure 1A shows an alternative capsule construction as employed in Examples 8 and 9.

Figure 2 shows a second embodiment where the pharmaceutically active material is contained within a recess in the back of the plug;

Figure 3 shows a typical drug release profile from a hole in the plug arrangement (Example 2);

Figures 4 and 5 show release profiles for embodiments having a tablet on the back of the plug (for Examples 6 and 8 respectively).

As shown in Figure 1 the capsule comprises a male plug 2 formed of a hydrogel material inserted in the neck 4 of the female body 6. The capsule is closed with a water-soluble cap 8.

The male plug 2 is formed of a hydrogel material, (such as disclosed in W090/09168) and is usually inserted so that the upper end of the plug is level with or below the end of the neck of the capsule body.

The water-soluble cap is preferably formed of gelatin. The capsule body may be formed of a water-insoluble material, which may be a water-insoluble plastics material, or may be gelatin coated with a water-impermeable coating.

A tablet 9 (whose size may be extended as shown in dotted lines) is adhered to the rear face 10 of the

hydrogel plug by means of a suitable adhesive which may be water-soluble, water-insoluble or pH sensitive. A water-soluble adhesive, might be polyvinylpyrrolidone or a gelatin-glycerol mixture. The tablet is located on the rear face of the plug so that it contacts the area of the plug which is least hydrated prior to disengagement of the plug. Also, sufficient clearance between the tablet and the capsule body should be provided to facilitate complete expulsion of the plug and tablet from within the body.

Figure 1A shows an alternative capsule construction as employed in Examples 8 and 9 wherein the neck region 4 is of reduced diameter and the upper end of the neck is flared.

Figure 2 shows a further embodiment which is useful where small amounts of pharmaceutical compositions are to be dosed. A recess 12 is provided in the rear inner face of the plug 2. The recess is generally cylindrical and has been formed by drilling. In one specific embodiment the hydrogel plug is 6.9mm in diameter and 3.0mm long. The recess is centrally located and is typically 3mm in diameter and sufficiently deep.

The recess is located in the last area of the hydrogel plug to swell. However, should limited hydration occur, this may be beneficial in widening the mouth of the recess and facilitating expulsion of the pharmaceutically active material.

In this case, the active material is in the form of a

paste or powder which has been filled into the recess. A layer 16 of a film forming material which is water-soluble, such as polyvinylpyrrolidone, is applied over the rear face of the plug so as to seal the pharmaceutical material into the recess. The plug is then inserted into the neck of the capsule in the normal way.

In use, the capsule is administered to a patient and passes into the stomach. The aqueous environment in the stomach quickly dissolves the water-soluble cap. Water is then absorbed into the hydrogel plug, which swells and is expelled from the capsule body after a predetermined time interval (for example 1 to 10 hours) carrying with it the pharmaceutically active material. The pharmaceutically active material then becomes exposed to the surrounding aqueous medium in the gastrointestinal tract and any water-soluble adhesive or retaining film is dissolved, leading to dissolution of the pharmaceutically active material.

In another embodiment the capsule is enteric-coated so as to pass through the stomach unaffected, and the coating dissolving in the intestine where the pH is relatively high.

As used herein, the term enteric coating includes all coatings (whether pH dependent or not) which are able to pass through the stomach and dissolve in the intestine. This includes coating materials, such as fats, which dissolve preferentially under the enzymatic regime

prevailing in the intestine.

The invention is useful inter alia for delivery of active material in the colon, where low levels of liquid are present.

EXAMPLES 1-5 (drug in hole in plug)

A number of in vitro experiments were carried out to evaluate release of pharmaceutically active drug from a hole drilled in the back of the hydrogel plug. Neat drug was introduced into the drilled hole and the hole sealed with a water-soluble polyvinylpyrrolidone and lactose paste. The plug was inserted into the capsule body either flush with the top of the neck of the body or recessed within the body. The amount of recessing strongly affects the release time. The body with inserted plug was then immersed in aqueous liquid and release of the drug into the liquid monitored spectrophotometrically. The results are shown in Table 1. A typical release profile (for Example 2) is shown in Figure 3, which illustrates the sharpness of the drug release.

TABLE 1 (hole in plug)

Example	Recess mm	Hole dia mm	Dose mg	*Mean Release time hrs
1	0.50	3.5	11	3.25 (85%)
2	0.58	3.5	2	4.1 (88%)
3	flush	3.5	2	2.1 (91%)
4	0.50	3.5	2	3.71 (95%)
5	0.50	2.5	5	3.79 (85%)

plug length = 4.0mm

plug dia = 6.90mm

drug = metoclopramide

hole depth = 1.5mm

* mean of 5-6 runs

figures in brackets are the mean % of drug released.

EXAMPLES 6 & 7 (tablet on back of plug)

Similar experiments were carried out for the arrangement wherein the drug is in the form of a tablet adhered to the back of the hydrogel plug. The adhesive used was a polyvinylpyrrolidone paste.

The results are given in Table 2 and a typical release profile (Example 6) is shown in Figure 4.

TABLE 2 (tablet on plug back)

Example	recess mm	dose mg	* mean release time hrs
6	flush	10	1.8 (109%)
7	0.50	10	3.94 (91%)

plug length = 4.0mm

" dia = 6.90mm

drug = promethazine hydrochloride

* mean of 4-6 runs

figures in brackets are the mean % of drug released.

EXAMPLE 8 (tablet on back of plug)

The release of quinine dihydrochloride from a tablet adhered to the back of a hydrogel plug was investigated.

(i) A quinine blend for tabletting was made up as follows (percentages by weight)

quinine dihydrochloride	86	wt.%
Avicel PH102	7.5	wt.%
Explotab	5	wt.%
sodium alkyl sulphate	0.5	wt.%
magnesium stearate	1	wt.%

Avicel (trademark) is a microcrystalline cellulose material available from FMC Corporation, USA. Explotab (trademark) is sodium-starch-glycollate and is available from Forum Chemicals, Reigate, U.K.

This blend was then mixed with other tabletting excipients as follows:

quinine blend (as above)	72 mg
sucrose	10 mg
Amberlite (trademark) resin	5 mg
	87 mg Total

The Amberlite (trademark) ion-exchange resin was ground to a powder in a pestle and mortar before use.

The mixture was then formed into a tablet 5mm in diameter and 4mm long using a hand tabletting press.

The sucrose and ion-exchange resin were included in the mixture as vehicles for attaching radioactive labels.

(ii) An adhesive paste was made up from the following ingredients:

polyvinylpyrrolidone (Plasdone K29/32)	30g
lactose	70g
water	30ml

A paste was made up from the polyvinylpyrrolidone and the water, to which the lactose was then added.

(iii) Each tablet was then adhered to the back of a hydrogel plug using a small amount of the adhesive paste. The plug dimensions are given in Table 3. Each hydrogel plug and tablet was fitted into the neck of a capsule body. The capsule body had a neck of reduced diameter compared to the rest of the body and the upper end of the neck was flared; as shown in Figure 1A. The plug was either flush or recessed below the upper end of the neck of the body and the tablet was on the inside of the plug. Each body was filled with a hydrogel powder which swells in contact with water and assists complete separation of the plug after disengagement from the body. A water-soluble gelatin cap was clipped over the neck of the body.

A pair of capsules (of nominal disengagement time 5hrs and 15hrs respectively) was then placed in a series of vessels each containing 1l of water at 37°C stirred by a paddle at 50rpm.

TABLE 3 (tablet on plug back)

Nominal disengagement time hrs	plug length mm	plug diameter mm	recess mm
5	4.25	6.85±0.05	flush
15	7	6.85±0.05	0.75mm

A stainless steel spring was fitted around the body of each capsule to weigh it down. Water from the vessel was circulated by a pump from the vessel into a UV cell (and then returned to the vessel) and the UV absorption at 254nm was monitored spectroscopically as a measure of quinine released into the water.

The results for six vessels are shown in Figure 5. In each vessel one capsule disengages at around 5 hrs and releases quinine into the water and the second capsule disengages at around 15 hrs and releases a further amount of quinine. It can be seen from the steep rise in the plots that rapid dissolution of the quinine occurs after disengagement.

EXAMPLE 9 (in vivo)

Eleven healthy volunteers (6 male, 5 female, and aged 20-29) who had fasted were each dosed by mouth with a controlled release capsule of the type shown in Figure 1A and described in Example 8 having a nominal disengagement time of 5 hrs. Each capsule contained a tablet adhered to the underside of the plug. The tablets were formulated as in Example 8 to contain a radiolabelled marker (Indium 111) bound to the Amberlite ion exchange resin to indicate the time and site of release of the tablet; together with quinine to enable absorption to be monitored.

Scintigraphic images of each volunteer were taken every half hour using a gamma radiation camera throughout

the study day to enable transit of the capsule through the gastro-intestinal tract and release of the radiolabelled marker to be monitored. Blood samples were also taken every half hour to monitor quinine absorption.

At 5 hours after dosing the capsules were located in the small intestine and colon. Prior to disengagement the scintigraphic image was small and bright. Release and subsequent dispersion of the tablet from the capsule was clearly seen by the spread of the radiolabelled marker. The average marker release time was 5.65 hours (standard deviation 0.67). This was confirmed by pharmokinetic data which indicated absorption of quinine into the plasma in all volunteers.

EXAMPLE 10 (Hydrogel plug production)

Hydrogel rods were prepared by polymerising 6,000 grams of polyethylene glycol PEG 8000 (Pharma) of number molecular weight Mn 8700 and ratio Mw/Mn = 1.03 (where Mw is the mean molecular weight) with 111.04 grams of hexanetriol, 506,8 grams of Desmodur W (dicyclohexylmethane-4,4-diisocyanate), and catalysed by 0.6 grams of anhydrous ferric chloride. The mole ratios were PEG 8000 (1 mole), hexanetriol (1.2 moles), Desmodur W (2.8 moles) and ferric chloride (0.01% by weight of PEG). The PEG 8000 was melted and dried to less than 0.05% w/w moisture content in a Buchi Rotavapor at 95°C, at a pressure less than 5 millibars for a period of two

hours. Then, the ferric chloride was dissolved in the hexanetriol at 75°C, and the mixture stirred into the dried PEG for 5 minutes at 100 rpm. The mixture at 85°C was then mixed with the Desmodur W by pumping into a mixer rotating at 1500 revolutions per minute. Molten polymer at about 80°C was then dispensed into tubular polytetrafluoroethylene moulds 25cm long under a vacuum of less than 50 millibars. Curing took place at 95°C for 4 hours in a fan equipped oven. The polymer rods were then allowed to cool.

The hydrogel rods are washed by immersion in a circulating stream of water containing butylated hydroxy anisole (BHA) as a stabiliser.

The washing removed water-soluble extractable substance from the polymer and the BHA stabiliser becomes incorporated into the polymer.

The swelling factor is defined as (Ws-Wd)/Wd x 100, where Ws is the swollen weight and Wd is the dry weight. The hydrogels were found to have a swelling factor of 270± 25.

The hydrogel rod was then cut into plugs, each generally of a nominal length 4mm, for use in the capsule of the invention as previously described.

CLAIMS

1. A controlled release capsule for delivering an active material, which comprises a male member (2) engaged within a neck portion (4) of a female body (6);

the capsule including a water-swellable material which swells so as to disengage the female body upon exposure of the capsule to an aqueous medium;

and a unit dosage (9) of said active material supported on either the male member or the female body, and the other thereof protecting the unit dosage from the aqueous medium prior to disengagement.

2. A capsule according to claim 1 wherein the male member is a plug engaged within the neck of the female body; the male plug being formed of the water-swellable material; and the unit dosage being supported on the male plug; the female body surrounding the unit dosage and protecting it from the aqueous medium prior to disengagement.

3. A capsule according to claim 2 which further comprises a recess in an inside end of the plug facing the body, the unit dosage of active material being provided in the recess.

4. A capsule according to claim 3 wherein the recess is in the form of a channel or channels.

5. A capsule according to claim 3 or 4 wherein the active material is sealed in the recess by a water-soluble material.

6. A capsule according to claim 2 wherein the unit dosage of active material is adhered to an inside end of the plug facing the female body.

7. A capsule according to claim 6 wherein the unit dosage of active material is in the form of a tablet.

8. A capsule according to claim 6 or 7 wherein the active material is adhered by means of a water-soluble adhesive.

9. A capsule according to claim 6 or 7 wherein the active material is adhered by means of a water-insoluble adhesive.

10. A capsule according to any preceding claim wherein the female body contains a material which expands in the presence of water to push apart the male member and the female body after disengagement thereof.

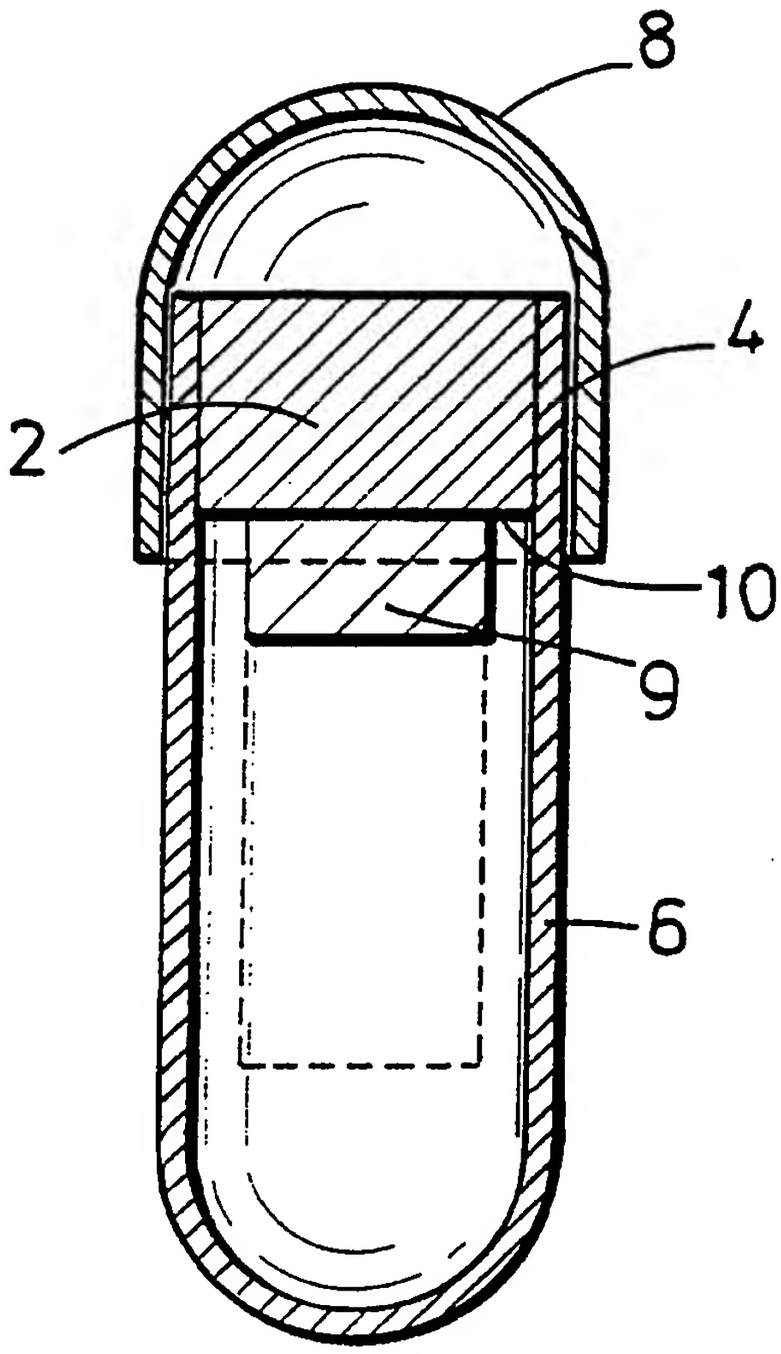

FIG. 1

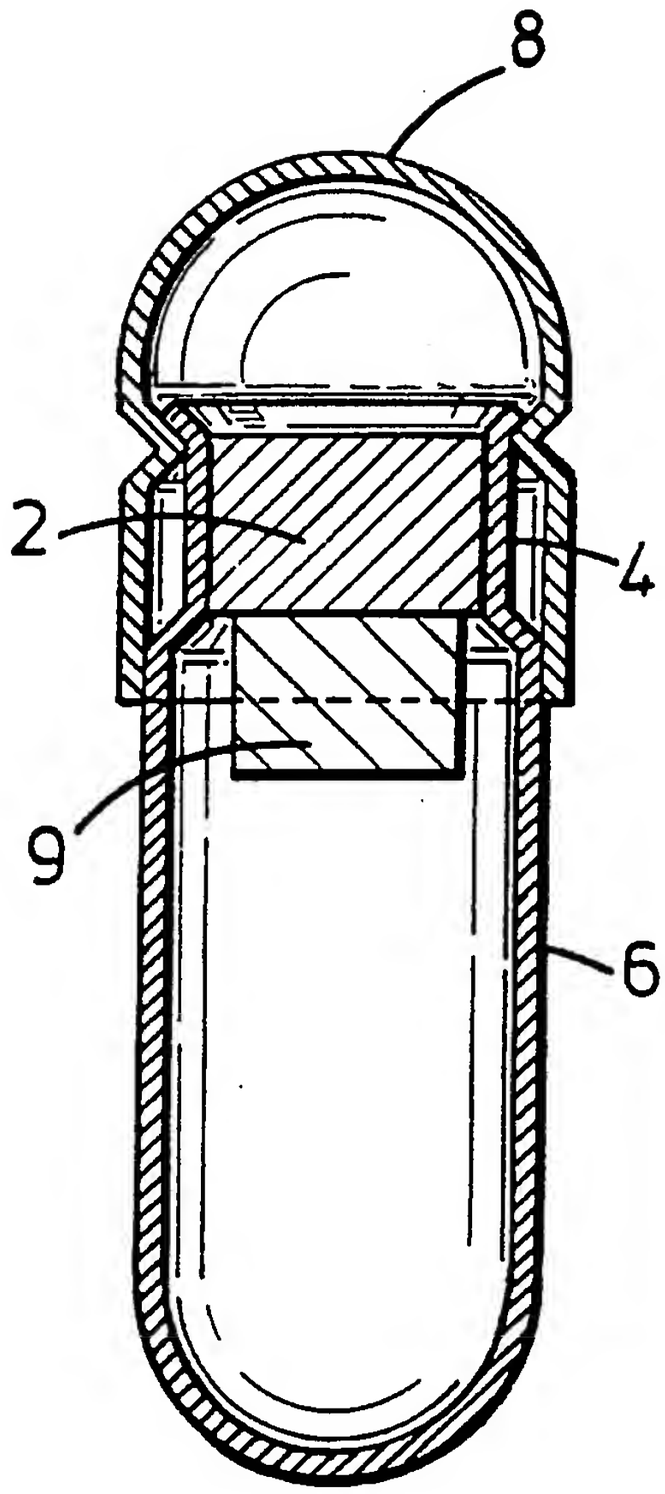

FIG. 1A

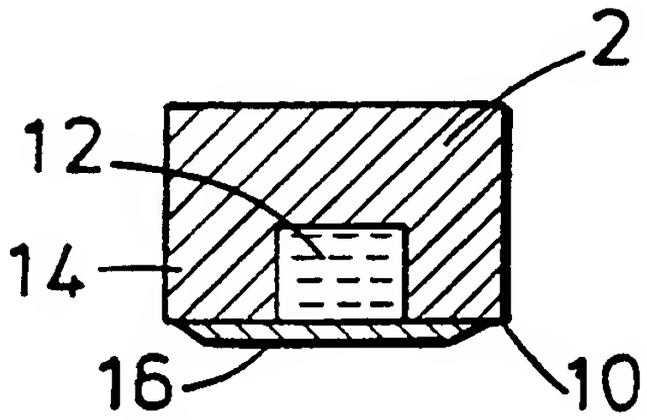

FIG. 2

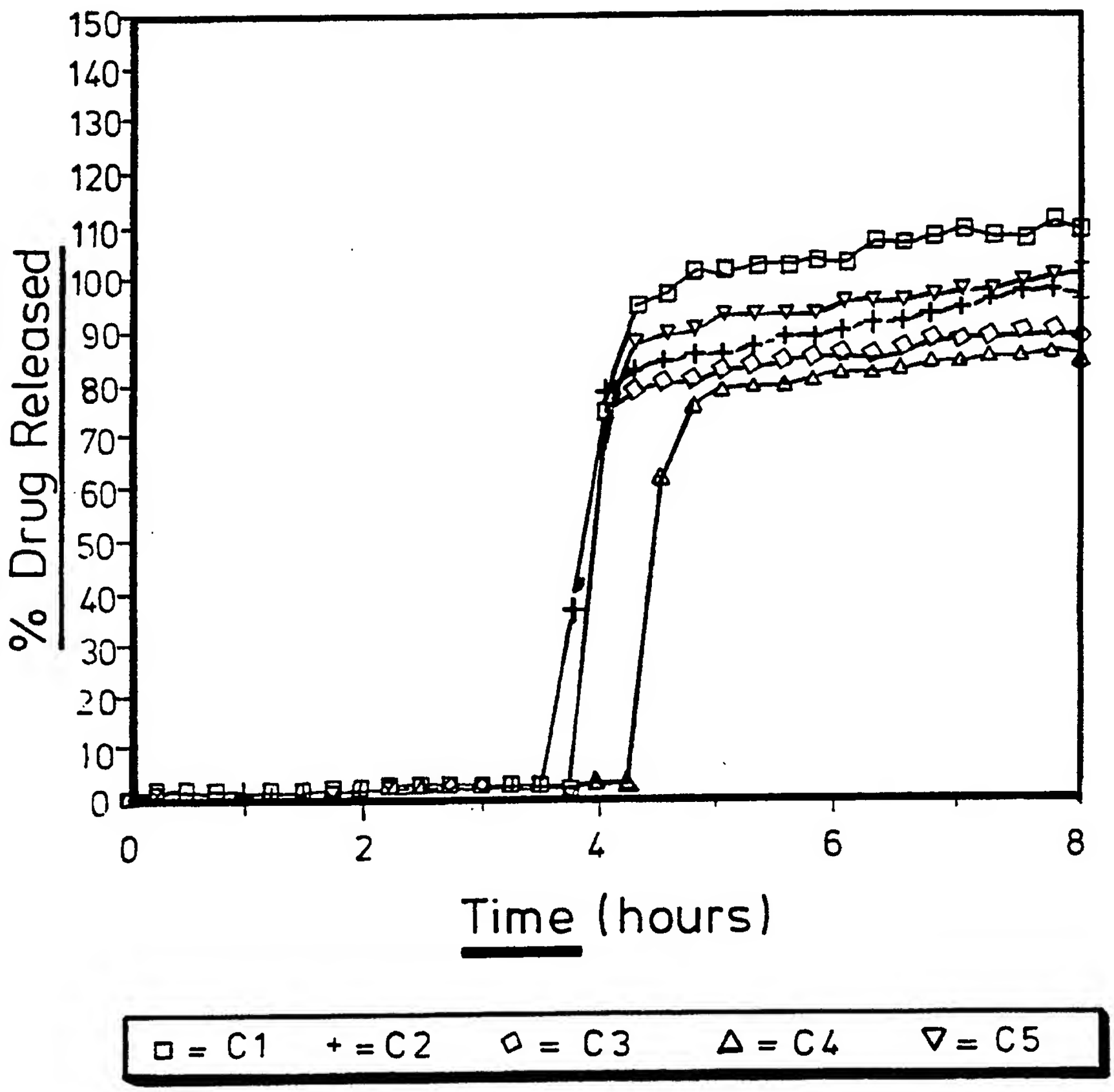
% Drug Released
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
Time (hours)
□ = C1
+ = C2
◇ = C3
△ = C4
▽ = C5

FIG. 3

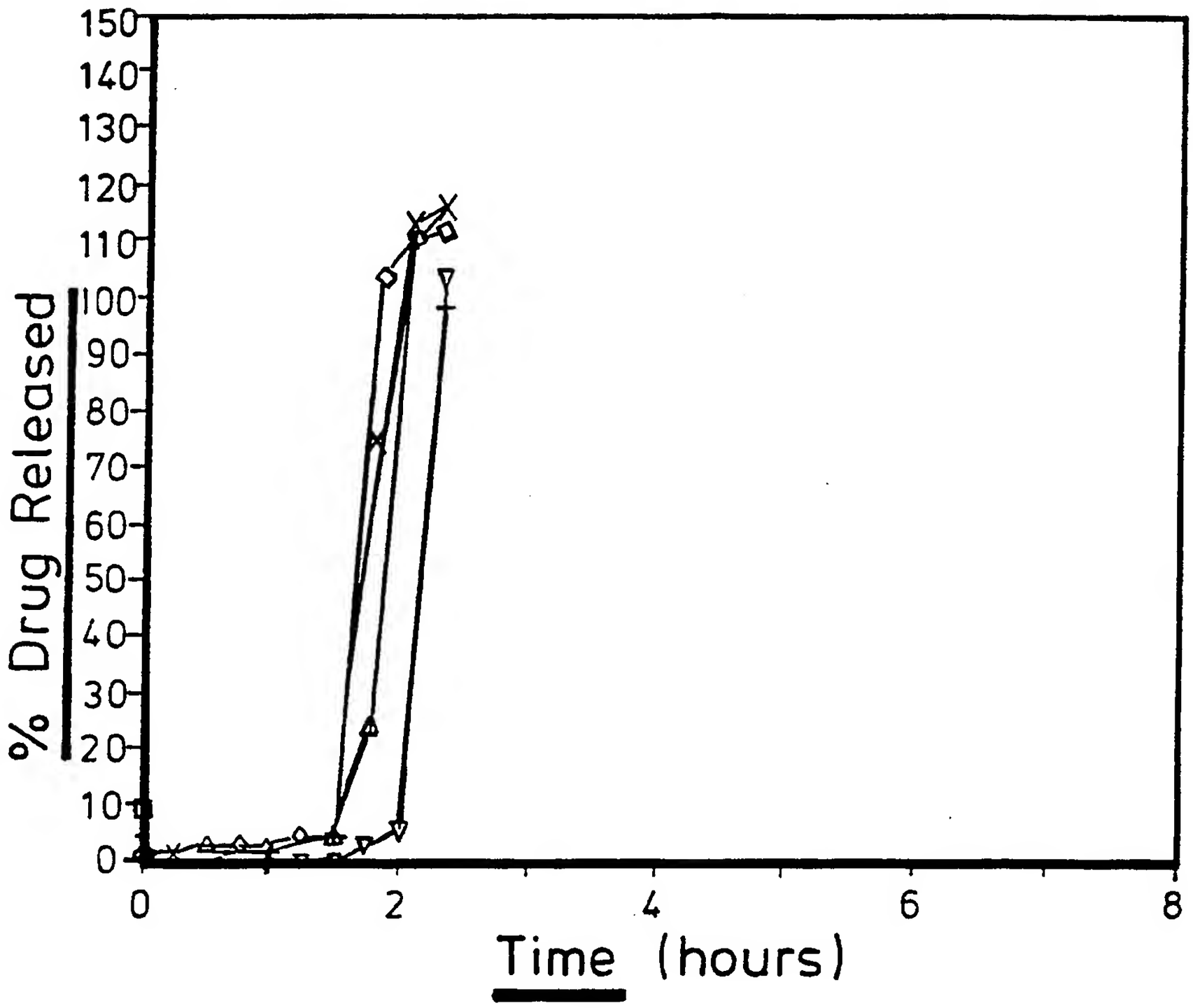
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
% Drug Released
0
2
4
6
8
Time (hours)
+ = C1
◇ = C2
Δ = C3
X = C4
∇ = C5

FIG. 4

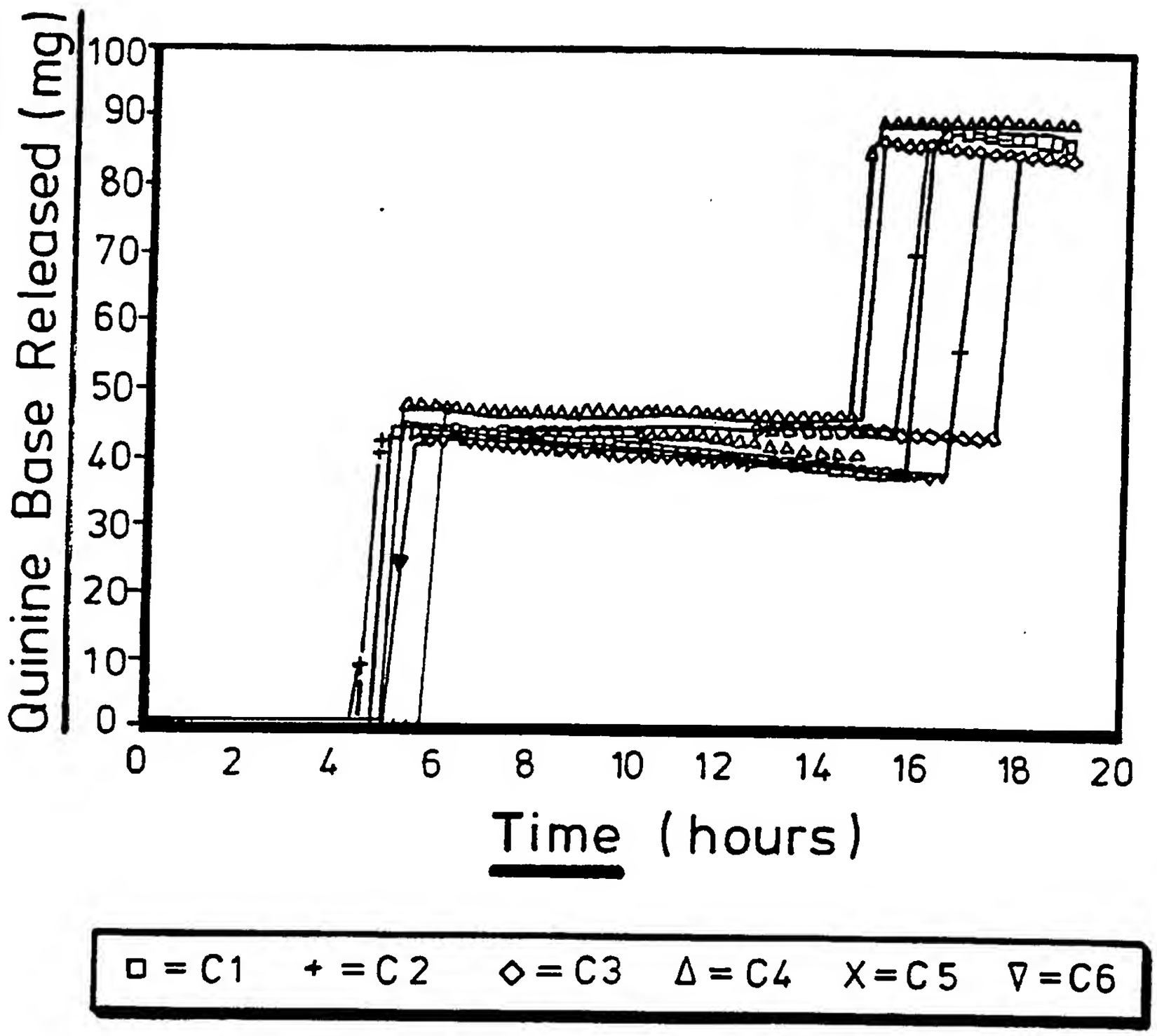
Quinine Base Released (mg)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
18
20
Time (hours)
□ = C1
+ = C2
◇ = C3
Δ = C4
X = C5
▽ = C6

FIG. 5

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 94/02468

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/48 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 384 646 (NATIONAL RESEARCH DEVELOPMENT CORPORATION) 29 August 1990 cited in the application	1
Y	see claims 1,3,5,7,9,10 see page 5, line 32 - page 6, line 3	2-10
Y	US,A,4 898 733 (RANDOLPH B. DEPRINCE, ET AL.) 6 February 1990 see claims 1-4 see column 4, line 55 - column 5, line 43	2-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 February 1995	23.02.95
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer VENTURA AMAT, A

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/GB 94/02468

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0384646	29-08-90	AU-B-	629915	15-10-92
		AU-A-	5163290	05-09-90
		EP-A-	0458887	04-12-91
		ES-T-	2043270	16-12-93
		WO-A-	9009168	23-08-90
		GB-A,B	2230442	24-10-90
		JP-T-	4505004	03-09-92
		US-A-	5342624	30-08-94
US-A-4898733	06-02-90	NONE		